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What goes in must come out—the small intestine modulates renal phosphate excretion*

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In a recent article in *PNAS*, Berndt *et al.* describe a novel and rapid regulation of renal phosphate excretion by phosphate instilled into the small intestine [1]. In a series of elegant experiments, renal phosphate clearance was measured before and during the infusion of a small amount of phosphate into the distal duodenum of rats. Twenty minutes after the infusion, massive phosphaturia was observed. This effect was specific for phosphate and was not seen when phosphate was instilled into the stomach or when NaCl was applied. Phosphaturia occurred without a measurable increase in serum phosphate and was independent of parathyroid hormone as it could also be observed in parathyroidectomized rats. Furthermore, other phosphaturic hormones, such as FGF23 and sFRP4, appear not to be involved. Alternatively, phosphaturia was preserved after denervation of the kidneys. Interestingly, infusion of a protein extract prepared from duodenum mucosa also induced phosphaturia similar to the intestinal phosphate infusion. Taken together, Berndt *et al.* suggest that upon phosphate ingestion, a phosphate-sensing mechanism in the duodenum releases a humoral signal which rapidly reduces renal phosphate reabsorption and thereby prevents an increase in the phosphate × calcium product, which otherwise would trigger precipitations, calcifications and secondary hyperparathyroidism.

Systemic phosphate homoeostasis is the product of regulated intestinal phosphate absorption from diet, deposition in skeleton, release from bone and soft tissue and tightly controlled renal reabsorption. Transport of phosphate in intestine, bone and kidney is mediated by several members of the type II sodium-dependent phosphate transporter family, SLC34, including the two renal isoforms NaPi-IIa and NaPi-IIc, and the intestinal NaPi-IIb transporter [2,3]. The importance of these transporters in phosphate balance has been highlighted by genetic knockout of NaPi-IIa in a mouse model [4] and more importantly, in patients with hereditary hypophosphataemic rickets with hypercalciuria caused by mutations in the NaPi-IIc (SLC34A3) transporter [5,6]. Serum phosphate concentration has to be maintained in a narrow range. Hypophosphataemia can cause skeletal deformities or osteomalacia, muscle weakness or glucose intolerance [7], whereas when phosphate rises, it will exceed the solubility limit of the calcium × phosphate product and precipitate. Consequences are tissue calcifications, arteriosclerosis or secondary hyperparathyroidism, as often seen in the setting of ESRD [8]. Under physiological conditions, phosphate balance is therefore tightly regulated by a number of hormones such as parathyroid hormone, 1,25 $(OH)_2$ vitamin D_3, or the growing number of so-called phosphatonins (including FGF-23, sFRP4 or FGF-7) [3,9,10]. These factors have in common that they regulate expression of renal and intestinal phosphate transporters and thereby determine absorption and excretion [3,9]. Additionally, it has long been known that dietary phosphate intake influences intestinal absorption and renal excretion through only poorly understood mechanisms. Chronic changes in dietary phosphate intake may involve at least in part 1,25$(OH)_2$-dependent changes in transporter expression [11]. Acute adaptation of renal reabsorption within hours leads to down-regulation of the renal NaPi-IIa transporter [12], an effect that can be mimicked in the renal OK cell line *in vitro* by adding phosphate to the medium [13]. These data strongly suggest the existence of a phosphate-sensing mechanism. The data by Berndt *et al.* point to an intestinal mechanism that would sense at the forefront of phosphate ingestion a potential phosphate load and acutely adapt renal excretion. This seems to make sense

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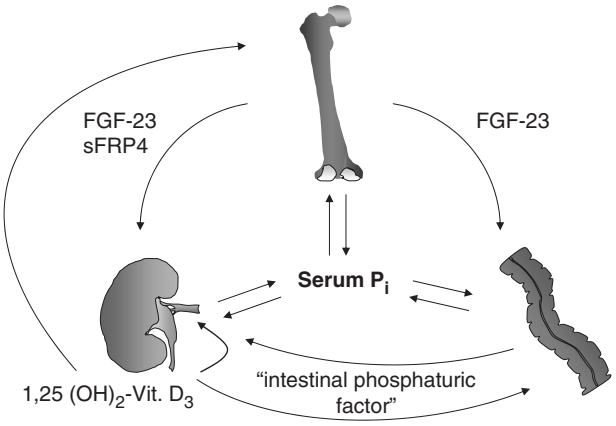

Fig. 1. Serum phosphate levels are determined by the rate of intestinal phosphate absorption, renal reabsorption and its deposition in bone or storage in soft tissue, respectively. Extensive cross-talk exists between bone and kidney via phosphaturic factors, such as FGF-23 or FRP4, and influences renal and intestinal expression of phosphate transporters. In addition, 1.25$(OH)_2$-vitamin D_3 modulates renal and intestinal phosphate transport and provides a feed-back loop to bone release of FGF-23. Parathyroid hormone directly inhibits renal phosphate reabsorption and stimulates renal synthesis of 1.25$(OH)_2$-vitamin D_3. The novel intestinal-renal axis may provide a means of balancing intestinal phosphate intake and renal excretion.

on the background that expression and activity of intestinal phosphate uptake transporters is only adapted slowly, reflecting long-term changes in dietary intake or hormonal status [14]. In contrast, the kidney can adapt rapidly to metabolic or hormonal alterations leading to acute internalization and degradation of NaPi-IIa cotransporters within 10–15 min [3,15]. Thus the body has two complimentary mechanisms that adapt to acute or chronic changes in dietary phosphate intake and thereby maintains phosphate perfectly within a safe range required by metabolism.

Deranged phosphate handling is a severe problem in patients with ESRD requiring dialysis. Reduced renal phosphate clearance causes phosphate retention with the precipitation of calcium-phosphate deposits in tissue and arteries, a major life-limiting complication in these patients. Moreover, intestinal phosphate absorption is inadequately high in these patients, and a rat model of chronic renal failure showed recently that expression of intestinal NaPi-IIb transporters is inappropriately normal [16]. Our understanding of how systemic phosphate homeostasis is regulated is at the very early stages. The recent discoveries of phosphaturic hormones and co-factors, such as FGF-23 and klotho, have added new complexity to the system [9,10,17]. However, if we aim to understand mechanisms that regulate systemic phosphate balance, we may ultimately also be able to devise strategies for the treatment of hyperphophataemia in ESRD patients. The discovery of an intestinal phosphate- sensing mechanism and the cross-talk with renal phosphate handling led to a number of interesting questions as to the nature of this putative 'phosphate-sensor' and its signal transduction to the kidney, the mechanism of inducing phosphaturia, and its potential role as a therapeutic target.

Conflict of interest statement. None declared.

References

1. Berndt T, Thomas LF, Craig TA *et al*. Evidence for a signaling axis by which intestinal phosphate rapidly modulates renal phosphate reabsorption. *Proc Natl Acad Sci USA* 2007; 104: 11085–11090
2. Murer H, Forster I, Biber J. The sodium phosphate cotransporter family SLC34. *Pflugers Arch* 2004; 447: 763–767
3. Murer H, Hernando N, Forster I, Biber J. Proximal tubular phosphate reabsorption: molecular mechanisms. *Physiol Rev* 2000; 80: 1373–1409
4. Beck L, Karaplis AC, Amizuka N, Hewson AS, Ozawa H, Tenenhouse HS. Targeted inactivation of Npt2 in mice leads to severe renal phosphate wasting, hypercalciuria, and skeletal abnormalities. *Proc Natl Acad Sci USA* 1998; 95: 5372–5377
5. Bergwitz C, Roslin NM, Tieder M *et al*. SLC34A3 mutations in patients with hereditary hypophosphatemic rickets with hypercalciuria predict a key role for the sodium-phosphate cotransporter NaP(i)-IIc in maintaining phosphate homeostasis. *Am J Hum Genet* 2006; 78: 179–192
6. Lorenz-Depiereux B, Benet-Pages A, Eckstein G *et al*. Hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in the sodium-phosphate cotransporter gene SLC34A3. *Am J Hum Genet* 2006; 78: 193–201
7. Brunelli SM, Goldfarb S. Hypophosphatemia: clinical consequences and management. *J Am Soc Nephrol* 2007; 18: 1999–2003
8. Coladonato JA. Control of hyperphosphatemia among patients with ESRD. *J Am Soc Nephrol* 2005; 16 [Suppl]2: S107–S114
9. Berndt T, Kumar R. Phosphatonins and the regulation of phosphate homeostasis. *Annu Rev Physiol* 2007; 69: 341–359
10. Wagner CA. Novel insights into the regulation of systemic phosphate homeostasis and renal phosphate excretion. *J Nephrol* 2007; 20: 130–134
11. Capuano P, Radanovic T, Wagner CA *et al*. Intestinal and renal adaptation to a low-Pi diet of type II NaPi cotransporters in vitamin D receptor- and 1alphaOHase-deficient mice. *Am J Physiol Cell Physiol* 2005; 288: C429–434
12. Levi M, Lötscher M, Sorribas V *et al*. Cellular mechanisms of acute and chronic adaptation of rat renal P_i transporter to alterations in dietary P_i. *Am J Physiol* 1994; 267: F900–F908
13. Pfister MF, Hilfiker H, Forgo J, Lederer E, Biber J, Murer H. Celular mechanisms involved in the acute adaptation of Na/Pi cotransport to high or low-P_i medium in OK cells. *Pflugers Arch* 1998; 435: 713–719
14. Radanovic T, Wagner CA, Murer H, Biber J. Regulation of intestinal phosphate transport. I. Segmental expression and adaptation to low-P(i) diet of the type IIb Na(+)-P(i) cotransporter in mouse small intestine. *Am J Physiol Gastrointest Liver Physiol* 2005; 288: G496–G500
15. Bacic D, Lehir M, Biber J, Kaissling B, Murer H, Wagner CA. The renal Na+/phosphate cotransporter NaPi-IIa is internalized via the receptor-mediated endocytic route in response to parathyroid hormone. *Kidney Int* 2006; 69: 495–503
16. Marks J, Churchill LJ, Srai SK *et al*. Intestinal phosphate absorption in a model of chronic renal failure. *Kidney Int* 2007
17. Kuro-O M. Klotho as a regulator of fibroblast growth factor signaling and phosphate/calcium metabolism. *Curr Opin Nephrol Hypertens* 2006; 15: 437–441

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